Hypertension Due to Co-existing Paraganglioma and Unilateral Adrenal Cortical Hyperplasia

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A rare case of combined unilateral adrenal hyperplasia and paraganglioma is reported. A 27-year-old woman presented with hypertension, palpitation, dizziness, and headache for about 3 months. Elevated plasma aldosterone with low renin and a high level of urine vanillylmandelic acid (VMA) were found. Computed tomography showed a microadenoma of the left adrenal gland and a well demarcated left retroperitoneal para-aortic mass. Adrenal vein sampling for aldosterone and renin levels suggested left adrenal lesion. Surgical removal of the left adrenal gland and para-aortic mass was performed. Pathologic examination of the resected left adrenal gland showed adrenal cortical hyperplasia and the left retroperitoneal para-aortic mass showed a paraganglioma. Postoperatively, blood pressure, plasma renin, aldosterone and urine VMA all returned to within normal ranges. The possible relationship of these two diseases is discussed. [J Formos Med Assoc 2007;106(12):1043–1047]

Key Words: adrenal hyperplasia, hyperaldosteronism, paraganglioma, pheochromocytoma

Secondary hypertension accounts for about 5% of high blood pressure cases. Hyperaldosteronism and pheochromocytoma are not uncommon causes of secondary hypertension, but the combination of these two diseases is rare. Here, we report a hypertensive patient who had unilateral adrenal hyperplasia with hyperaldosteronism and paraganglioma (extra-adrenal pheochromocytoma).

Case Report

A 27-year-old woman was referred to the cardiology clinic for evaluation of her hypertension. She was previously healthy until about 3 months ago when she suffered from palpitation, dizziness and headache. High blood pressure of up to 237/131 mmHg was recorded when she visited our emergency department for an episode of abdominal discomfort. Thereafter, she reported systolic blood pressure 167–170 mmHg and diastolic blood pressure 118–132 mmHg measured at home. She had heat intolerance but denied facial flush. None of her family members has hypertension. Plasma aldosterone level was 711 pg/mL (78–104 pg/mL in sitting position) and renin level was 15 pg/mL (16–58 pg/mL in sitting position). Spironolactone 25 mg q.d. and bisoprolol 5 mg q.d. were prescribed, and blood pressure was controlled at about 130/90 mmHg.

When she was hospitalized for further evaluation, she was afebrile, her blood pressure was...
148/87 mmHg, pulse rate was 72 beats/min, and respiratory rate was 18/min. She had no Cushing’s appearance such as truncal obesity, moon face, hirsutism, or fat deposits over the posterior neck. Physical examination of the heart revealed normal heart rate and no murmurs, and the lungs were clear to auscultation bilaterally. The abdomen was soft and nontender on examination, without bruit. Radial, femoral and dorsalis pedis pulses were present and symmetric bilaterally. Extremities were without edema, cyanosis, clubbing or bruising.

Electrocardiogram and chest radiograph were unremarkable. Her complete blood count was normal. Her biochemistry profile showed: Na, 141 mmol/L; K, 4.6 mmol/L; Cl, 103 mmol/L; total cholesterol, 254 mg/dL; and triglyceride, 115 mg/dL. The 24-hour urine revealed vanillylmandelic acid (VMA) level of 13.1 mg/day (1.0–7.5), epinephrine of 4.4 µg/day (0–22.4), norepinephrine of 430.6 µg/day (11.1–85.5), and dopamine of 221.2 µg/day (50–450).

Abdominal computed tomography showed a 0.67-cm bulging nodule at the medial limb of the left adrenal gland, and a 4.2-cm well demarcated heterogeneous, left retroperitoneal para-aortic mass, suggesting an extra-adrenal pheochromocytoma (Figure 1). Magnetic resonance imaging showed the same para-aortic tumor but no evidence of left adrenal microadenoma. Adrenal vein sampling for aldosterone and renin suggested hyperaldosteronism of left adrenal origin (Table).

Left adrenalectomy and excision of the left retroperitoneal tumor was performed smoothly. The resected left adrenal gland showed focal cortical hyperplasia with preserved zonal architecture and no definite tumor was found (Figures 2B–D). The retroperitoneal mass measured 5.0 × 5.5 × 3.0 cm in size and 35.0 g in weight, and was firm and well-demarcated. Microscopically, it showed sheets or acini bland-appearing tumor cells in delicate fibrovascular stroma. The tumor cells had abundant finely granular basophilic or amphophilic cytoplasm with bizarre hyperchromatic and pleomorphic nuclei. It was confirmed as a paraganglioma (Figure 2A). After the operation,
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her blood pressure returned to normal without the use of antihypertensive medication, and her plasma aldosterone, renin and urine VMA levels all returned to within normal ranges (71.96 pg/mL, 48.32 pg/mL, and 3.30 mg/day, respectively).

Discussion

The simultaneous occurrence of extra-adrenal pheochromocytoma and unilateral adrenal cortical hyperplasia is extremely rare. Only two cases have previously been reported in the English literature.\(^1,2\) The relationship between these two conditions is not known. Based on the coexistence of adrenal pheochromocytoma and cortical adenoma, some authors have postulated that the interaction of contiguous adrenal medullary and cortical tissues may exist, and catecholamine (or other substance) secreted by pheochromocytoma will stimulate cortical hyperplasia and subsequently adenoma formation.\(^3,4\) However, whether this interaction exists between extra-adrenal pheochromocytoma and adrenal cortex remains unclear. Madison showed that it was epinephrine, not norepinephrine, that stimulated ACTH release and induced hyperplasia of the adrenal cortex in an experimental animal model.\(^5\) Since most extra-adrenal pheochromocytomas secrete norepinephrine,\(^6\) as in this case, the coexistence of extra-adrenal pheochromocytoma and adrenal cortical hyperplasia may be coincidental. Occasionally, pheochromocytoma is accompanied by elevated plasma renin activity, leading to secondary hyperaldosteronism (epinephrine has greater renin-stimulating activity than norepinephrine).\(^7,8\) Hsieh et al thought that chronic secondary hyperaldosteronism may lead to the

Figure 2. (A) Histologic section of the extra-adrenal paraganglioma shows cells with abundant finely granular basophilic or amphophilic cytoplasm; bizarre hyperchromatic and pleomorphic nuclei are also noted (hematoxylin & eosin, 400×). The resected left adrenal gland: (B) zona glomerulosa; (C) zona fasciculate; (D) zona reticularis. There is only focal cortical hyperplasia, and no tumor is seen (hematoxylin & eosin, 400×).
development of autonomous aldosterone excess and adenoma formation; as aldosterone secretion increased and body fluid expanded, renin secretion would be suppressed. However, in this case, if the adrenal abnormality is caused by extra-adrenal paraganglioma secreting substance, it should be bilateral, not unilateral. Gordon et al also suggested that the simultaneous presence of pheochromocytoma and primary aldosteronism is probably a chance occurrence.

The symptoms of palpitation and headache in this patient could be induced by paraganglioma (extra-adrenal pheochromocytoma). Pheochromocytoma is a catecholamine-secreting tumor that arises from chromaffin cells. Because most chromaffin cells degenerate after birth, with the exception of those in the adrenal medulla, most pheochromocytomas (85–95%) are found in the adrenal gland. Extra-adrenal pheochromocytoma occur most commonly in the organ of Zuckerkandl (75%) as in this case, but may also be found in the thorax, abdomen, pelvis, mediastinum and neck. Pheochromocytomas that secret epinephrine are particularly likely to be found in the adrenal medulla. Extra-adrenal paragangliomas rarely secret epinephrine. This is due to their lack of immediate proximity to the adrenal cortex, which ordinarily provides the high concentrations of cortisol needed for induction of the enzyme phenylethanolamine-N-methyl-transferase (PNMT), which catalyzes the conversion of norepinephrine to epinephrine. If the predominant secretion of the tumor is epinephrine, the symptoms will reflect its effect, mainly systolic hypertension caused by increased cardiac output, tachycardia, sweating, flushing, and apprehension. If norepinephrine is predominately secreted, as from some adrenal tumors and from almost all extra-adrenal tumors, the symptoms will include both systolic and diastolic hypertension from peripheral vasoconstriction but less tachycardia, palpitation and anxiety. There was no tachycardia, sweating or facial flushing in this case, but there was systolic and diastolic hypertension. These findings suggest that the main hormone secreted in this patient was norepinephrine, which was compatible with urine catecholamine analysis.

The serum potassium level of this patient was not checked initially, and it was 4.6 mmol/L after taking spironolactone. She had no symptoms induced by hypokalemia such as muscle weakness. However, classical features of hypokalemia and metabolic alkalosis can be absent even in the presence of marked hypertension. Recent evidence suggests that the prevalence of primary hyperaldosteronism is higher than originally thought. In an Australian tertiary practice, Hamlet et al found that the majority of patients (70%) with primary aldosteronism were normokalemic.

Primary aldosteronism is usually caused by an aldosterone-producing adenoma or bilateral adrenal hyperplasia that comprise about 65% and 30% of cases, respectively. However, 5% of primary aldosteronism are caused by other etiology such as unilateral adrenal hyperplasia—a relatively rare subset of adrenal hyperplasia with an approximate prevalence of less than 1% of all cases of primary aldosteronism. Unilateral adrenal hyperplasia usually mimics unilateral adrenal adenoma and is difficult to diagnose before resection. Computed tomography is unreliable in diagnosing patients with unilateral adrenal hyperplasia. Goh et al found that computed tomographic examination correctly localized unilateral adrenal hyperplasia in 53% (9/17) of patients; in contrast, adrenal vein sampling is the most accurate test, which localized the lesion side successfully in all patients (22/22) in whom it was performed. Unilateral adrenal hyperplasia can present with normokalemia, and it is probably an early phase of the transformation between hyperplasia and adenoma. Shigematsu et al, who studied mRNA expression for steroidogenic enzymes in adrenal cortices, also postulated that adrenal micronodules might ultimately become adenoma by repeated growth and fusion.

We reported a case of secondary hypertension caused by extra-adrenal paraganglioma and left adrenal cortical hyperplasia. The combination of these two conditions is unusual and the interaction
between them remains uncertain. Further investigation is needed.

References